Translational Neurodegeneration

REVIEW Open Access

Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease

Zhi-Kun Sun[1†], Hong-Qi Yang[1†] and Sheng-Di Chen[2*]

Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disorder, characterized clinically by insidious onset of memory and cognition impairment, emergence of psychiatric symptoms and behavioral disorder, and impairment of activities of daily living (ADL). Traditional Chinese medicine (TCM) is practiced in the Chinese health care system for more than 2,000 years. In recent years, scientists have isolated many novel compounds from herbs, some of which improve dementia with fewer side effects than conventional drugs and are regarded as potential anti-AD drugs. In this review, we summarize the latest research progress on TCM showing their possible role of treatment of AD and other demented diseases and possible pharmacological actions.

Keywords: Alzheimer's disease, Chinese traditional medicine, Therapeutic approach

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder, characterized clinically by insidious onset of memory and cognition impairment, emergence of psychiatric symptoms and behavioral disorder, and loss of activities of daily living (ADL). The histopathological hallmarks of AD include the formation of senile plaques (SP), neurofibrillary tangles (NFTs) and the loss of neurons. With the rapid increase in the aged population in recent years, senile dementia has become one of the world's important public health issues. AD is the most common type of senile dementia. It is estimated that the prevalence of AD over the age of 85 may be as high as 25 ~ 50%, and AD is increasingly being recognized as one of the most important medical problems in the elderly. It is very important to identify novel and pharmacotherapeutic drugs for AD. Traditional Chinese medicine (TCM) is practiced in the Chinese health care system for more than 2,000 - years. Many active pharmacological compounds from Chinese herbal medicines have been identified for the treatment of various diseases. In recent years, scientists have isolated many novel compounds from herbs, some of which improve dementia with fewer side effects than conventional drugs and are regarded as potential anti-AD drugs. In this review, we summarize the latest research progress on Chinese herbal medicines showing their roles of treatment of AD and other demented diseases and possible pharmacological actions.

* Correspondence: chen_sd@medmail.com.cn
†Equal contributors
[2]Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200025, People's Republic of China
Full list of author information is available at the end of the article

Huperzine A

Huperzine A (HupA) is an extract of Huperzia serrata, it has been used for centuries in China to treat fever, swelling, and blood disorders. HupA is a potent, reversible, and selective inhibitor of acetylcholine esterase, exhibiting rapid absorption and penetration into the brain in animal studies, and it has been widely used in China for the treatment of AD. HupA was reported to reduce glutamate-induced toxicity in neurons, possibly through modulation of glutamate-NMDA receptor interaction, or of the passage of Ca2+ through associated ion channels [1]. In addition to the hypothesized reduction in excitotoxicity, other neuroprotective and antioxidant properties have been suggested as well [2]. A recent discovery from Yang et al. verified the co-occurrence of the beneficial effects of HupA on mitochondrial dysfunction and memory deficits in APP/PS1 double transgenic mice, at a time point that AChE was not inhibited [3].

Another study indicates that HupA treatment can significantly ameliorate the loss of dendritic spine density and synaptotagmin levels in the brain of APP/PS1 transgenic mice, and this neuroprotection was associated with reduced amyloid plaque burden and oligomeric beta-amyloid (Abeta) levels in the cortex and hippocampus [4]. HupA can improve triple transgenic mice (3xTg-AD) learning and memory in the Morris water maze and some indicators of emotionality without inducing important adverse effects. Moreover, HupA activate protein kinase C/mitogen-activated protein kinase pathway signalling, alpha-secretases (ADAM 10 and TACE) and increase the fraction of phospho-glycogen synthase kinase 3-beta in 3xTg-AD mice [5]. And it could activate Wnt signaling and reduce amyloidosis in APP/PS1 transgenic mice brain [6].

In a meta-analysis of the efficacy and safety of HupA in AD, The author searched for randomized trials comparing HupA with placebo in the treatment of AD. The primary outcome measures were mini-mental state examination (MMSE) and ADL. Data were extracted from four randomized clinical trials and analyzed using standard meta-analysis and meta-regression methods. Oral administration of HupA for 8–24 weeks (300–500 μg daily) led to significant improvements in MMSE and ADL. Most adverse events were cholinergic in nature and no serious adverse events occurred [7]. However, another study assessed the safety, tolerability, and efficacy of HupA in mild to moderate AD in a multicenter trial in which 210 individuals were randomized to receive placebo (n = 70) or HupA (200 μg BID [n = 70] or 400 μg BID [n = 70]), for at least 16 - weeks, with 177 subjects completing the treatment phase. This study provides evidence that HupA 200 mg BID has no demonstrable cognitive effect in patients with mild to moderate AD [8]. A randomized, multicenter trial in China showed that in a 12 weeks treatment period (400 μg/QD), HupA improved 4.6 points in cognition assessed by ADAS-Cog, 2.7 points by MMSE and 2.4 points by ADL in comparison with baseline data. Only mild and transient adverse events (edema of bilateral ankles and insomnia) were observed in 3% of huperzine treated patients. These results indicated its safety and effective in AD treatment [9].

Gingko biloba

The Ginkgo tree is indigenous to Korea, Japan, China, now it can be found worldwide. Extracts from Ginkgo biloba have been used medicinally in TCM for thousands of years to treat circulatory problems, asthma, vertigo, fatigue, and tinnitus. Ginkgo biloba has been used traditionally in Iran to improve memory loss associated with blood circulation abnormalities. Recently, it has become more widely used in the United States to treat age-related physical and cognitive disorders. The Ginkgo biloba extract EGb 761 has shown favourable effects on cerebral circulation and neuronal cell metabolism, on the muscarinic cholinergic system, and showed antioxidant activity [10]. EGb761 was also neuroprotective against Abeta- and NO-induced toxicity in vitro [11], and could reduce apoptosis both in vitro and in vivo [12]. Using hippocampal neuronal cultures, Shi et al. found EGb761 can block Abeta1-42-induced Ca^{2+} dyshomeostasis mediated by formation of toxic mediators such as H_2O_2 and PAF [13].

Treatment with Ginkgo biloba extracts attenuated scopolamine-induced amnesia in rats, enhanced memory retention in young and old rats and improved short-term memory in mice [14]. The clinical efficacy of Ginkgo biloba extracts, including EGb 761, was observed (modest improvements in cognitive function) following administration to AD and non-AD patients in various studies [15,16]. In a 24-week randomised controlled trial, using 240 mg once-daily preparation of Ginkgo biloba extract EGb 761 in 404 outpatients, EGb 761 can improve cognitive functioning, neuropsychiatric symptoms and functional abilities in AD and VaD [17]. However, in Ginkgo Evaluation of Memory (GEM) study, a randomized, double-blind, placebo-controlled clinical trial of 3069 community-dwelling participants aged 72 to 96 years, with a median follow-up of 6.1 years, Snitz et al. reported that the use of G. biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment [18], Which results has the negative study and it different from the results studied before. We thought the reason is the Participants in that study chosed are the older adults with MCI and not AD or VD. It is apparent that G. biloba can be useful in the treatment of AD symptoms, but further research is necessary to identify appropriate dosing regimens. Moreover, the potential effects of long-term use, interactions with other medicines, and standardization of extracts must be a consideration.

Curcumin

Curcuma longa is a member of the ginger family indigenous to South and Southeast Asia, where it is grown commercially. Turmeric is derived from the rhizome (root) of the plant, whose most important commercial application is curry. Curcumin was isolated in 1815, initially named diferuloylmethane. Preparations made from Curcuma longa have been used for centuries in ayurvedic medicine to treat a variety of ailments. These may be taken orally for dyspepsia, liver disease, flatulence, urinary tract disease, as a "blood purifier," or used topically for a variety of skin ailments. In vitro and in vivo evidence has suggested several possible mechanisms of its action relevant to AD, such as, anti-oxidant, anti-inflammatory properties, and a

direct effect against Abeta aggregation [19,20]. Several animal studies suggest that this agent may reduce oxidative damage and amyloid pathology in Alzheimer transgenic mice and may modulate amyloid-induced cytopathology or macrophage processing of amyloid [21]. In rat model of sporadic dementia of Alzheimer's type, curcumin can ameliorate the cognitive deficits and neurodegeneration [22]. In our previous studies, we found that curcumin showed obvious inhibitory effect on the apoptosis induced by Abeta(25–35) [23]. In another report, we also found that curcumin suppressed activated astroglia induced by Abeta and it might act as a PPARgamma agonist to inhibit the inflammation in Abeta-treated astrocytes [24]. Curcumin can inhibit Abeta-induced cytotoxicity in primary prefrontal cortical neurons by MTT and TUNEL assays. Curcumin also corrected Abeta-induced caspase-3 activation, Bcl-2 downregulation and Akt phosphorylation [25]. In a 24-week randomized, double blind, placebo-controlled study, curcumin was generally well-tolerated though three subjects on curcumin withdrew due to gastrointestinal symptoms. But the researchers were unable to demonstrate clinical or biochemical evidence of efficacy of curcumin in AD in this 24-week placebo-controlled trial though preliminary data suggested limited bioavailability of this compound [26]. However, No clinical trials of curcumin in AD patients have been proved to be valid, the reason that curcumin has not been a miracle cure is that it is poorly absorbed in humans, and its use as a treatment for AD is currently under investigation.

Salidroside

The rhizome of Rhodiola rosea L has been used in East Asia as a tonic and anti-aging agent since ancient times. There has been mounting evidence that the extract from the rhizome of Rhodiola rosea L possesses significant neuroprotective activity and antioxidative effects. Salidroside is one of the major compounds from the water extracts of the rhizome of Rhodiola rosea L. In a previous study, salidroside could significantly inhibite O_2^--or H_2O_2-induced neurotoxicity in rat hippocampal neurons. Several in vitro studies shown that salidroside can protect Abeta-induced oxidative damage on rat neuronal PC12 cells and on SH-SY5Y human neuroblastoma cells [27]. In a in vivo study, salidroside can protect hippocampal neurogenesis against streptozotocin-induced neural injury in rat [28]. In our previous studies, we found that salidroside was able to attenuate abnormal processing of amyloid precursor protein by decreased BACE1 protein level and promoted the secretion of sAPPalpha in hypoxic condition in SH-SY5Y cells [29]. However, other study showed that salidroside has no neuroprotective effects on neuronal cell death induced by Abeta in PC12 cells [30]. Further studies are needed to confirm the effect of salidroside in AD treatment.

Periwinkle-vinca minor (vinpocetine)

Periwinkle has historically been used to treat a wide variety of diseases. It was used as a folk remedy for diabetes in Europe for centuries. In India, juice from the leaves was used to treat wasp stings. In Hawaii, the plant was boiled to make a poultice to stop bleeding. In China, it was used as an astringent, diuretic, and cough remedy. In Central and South America, it was used as a homemade cold remedy to ease lung congestion and inflammation, as well as sore throats. Numerous mechanisms of action have been proposed for vinpocetine; it has been reported to improve cerebral metabolism, increase glucose and oxygen consumption by the brain, and improve brain resistance to hypoxia [31]. A neuroprotective effect has been claimed through blocking voltage-gated sodium channels, modulating neurotransmitter release, and potentiating the effect of adenosine in cytotoxic hypoxia [32]. Vinpocetine has been reported to have a variety of actions that would hypothetically be beneficial in AD. vinpocetine can ameliorate intracerebroventricular streptozotocin induced cognitive dysfunction and oxidative stress[33]. Several double-blind studies have evaluated vinpocetine for the treatment of AD and related conditions [34]. The best of these was a 16-week double-blind placebo-controlled trial of 203 people with mild to moderate dementia, in which vinpocetine significantly benefit the treated group [34,35]. Meta-analysis of older studies of vinpocetine in poorly defined dementia populations concluded that there is insufficient evidence to support its clinical use at this time.

Centella asiatica L

Centella asiatica leaf is an ancient Ayurvedic remedy, which is used as a revitalizing herb that strengthens nervous function and memory. It is reported to restore youth, memory and longevity [36]. The herb is also taken as a tonic for poor digestion and rheumatism; the latter suggest it may have anti-inflammatory effects. Centella asiatica is also used in TCM for combating physical and mental exhaustion [37]. In mice, an extract of Centella asiatica leaf was sedative, antidepressant and showed cholinomimetic activity, which was blocked by atropine. These results indicate that Centella asiatica may be appropriate to treat symptoms of depression and anxiety in AD, and may also enhance cholinergic activity and thus, cognitive function. An aqueous extract of Centella asiatica leaf improved learning and memory processes in rats, and modulated dopamine, 5-hydroxytryptamine (5-HT) and noradrenaline systems in rat brain in vivo [38]. The triterpene asiatic acid and its derivatives have been shown to protect cortical neurons from glutamate-induced excitotoxicity in vitro [39]. In the brains of APP/PS mice, Centella asiatica extract can impact the amyloid cascade altering amyloid beta

pathology and modulating components of the oxidative stress response that has been implicated in the neurodegenerative changes that occur with AD [40]. In an intracerebroventricular streptozotocin model of AD, Centella asiatica extract is effective in preventing the cognitive deficits, as well as the oxidative stress in rats [41]. In another in vivo study, Centella asiatica extract can significantly attenuate intracerebroventricular colchicine-induced cognitive impairment and associated oxidative damage in rat. Further studies are necessary to confirm this to identify any potential relevance in AD treatment.

Melissa officinalis L

Melissa officinalis (Labiatae) leaf has been used as a medicinal plant for more than 2000 years. In traditional European medicine, Melissa officinalis was used as a calming and strengthening remedy and to treat migraines, melancholia, neuroses and hysteria, and the plant has been acclaimed for promoting long life and for restoring memory [42]. The primary monoterpenes identified in the essential oil of Melissa officinalis include citral (geranial and neral) [43] which is a weak inhibitor of AChE [44]. Melissa officinalis has been the subject of research regarding its potential as sedative and anxiolytic activities that may be appropriate to provide symptomatic relief for behavioural problems such as agitation in AD. Other activities of Melissa officinalis leaf extracts that may be useful for AD therapy include antioxidant effects [45] and binding to muscarinic and nicotinic receptors in vitro [46], which suggests that favourable effects on cholinergic function may occur in AD patients. In some studies, Melissa officinalis can reduce the cognitive deficits and has a good sedative effect in patients with AD [47]. Previous clinical studies showed that the extract of Melissa officinalis reduces laboratory-induced stress [48] and might have benefits in mood improvement [49]. The use of these herbs and formulations should be well tolerated and adverse effects have not yet been reported. Further studies should be conducted to compare the current therapies for AD and the use of these herbal remedies in controlling the symptoms of AD.

Polygala tenuifolia willd

Polygala tenuifolia (Polygalaceae) root is used in TCM as a cardiotonic and cerebrotonic, as a sedative and tranquillizer, and for amnesia, forgetfulness, neuritis, nightmares and insomnia [50]. According to the Chinese Materia Medica, the root is supposed to have a special effect upon the will and mental powers, giving strength of character, improving understanding, strengthening the memory, and increasing physical powers. There have been numerous studies regarding the reputed memory enhancing potential of Polygala tenuifolia root. For example, the traditional Chinese prescription DX-9386, composed of four herbs (Panax ginseng, Polygala tenuifolia, Acorus gramineus and Poria cocos) has shown favourable effects in relation to AD symptoms in several animal models. Tenuifolin inhibited amyloid-beta secretion in vivo and vitro [51]. DX-9386 improved motor activity, reduced lipid peroxidation, ameliorated memory impairment and prolonged the lifespan of senescence accelerated mice and, ameliorated the ethanol- and scopolamine-induced memory impairment in mice [52,53]. Further investigations are required to clarify the contribution of each of the four herbs in DX-9386 to the observed pharmacological activities. GEPT, consisting of extracts from ginseng, epimedium, polygala, and tuber curcumae [54], has shown valuable for the treatment of AD. In the brain of APPV717I transgenic mice, GEPT can reduce the level of Abeta via the inhibition of γ-secretase (presenilin-1) and the promotion of insulin-degrading enzyme and neprilysin [55]. It can also increases synaptophysin expression in APPV717I transgenic mice. [56]. Kami-utan-to (KUT), a prescription containing 13 herbs including Polygala tenuifolia root, is used in traditional Japanese medicine to treat psychoneurological diseases. KUT dose-dependently upregulated choline acetyltransferase (ChAT) activity and increased nerve growth factor (NGF) secretion in vitro, and improved passive avoidance behaviour and induced ChAT activity in the cerebral cortex of aged rats, and in scopolamine-induced memory impaired rats in vivo [44,57]. The effects on ChAT activity and NGF secretion in vitro were not as pronounced when treated with KUT in the absence of Polygala tenuifolia root, but Polygala tenuifolia root extract alone did upregulate ChAT activity and increase NGF secretion in vitro. These results suggest that Polygala tenuifolia root, particularly the cinnamic acid derivatives, significantly contribute to the pharmacological activities of KUT, and may explain the reputed beneficial effects of KUT in Japanese medicine.

Salvia miltiorrhiza bung

Throughout history Salvia miltiorrhiza (Labiatae) has been used for the treatment of a variety of medical conditions. The dried root of Salvia miltiorrhiza was used in folk medicine for the management of blood disorders. It is prescribed in TCM to stabilize the heart and calm nerves. Official indications for the root include treatment of blood circulation disorders, insomnia, neurasthenia and alleviation of inflammation [58]. Salvia miltiorrhiza root may inhibit neuronal cell death by inhibition of presynaptic glutamate release, and nitric oxide (NO) formation. Other investigations indicate Salvia miltiorrhiza root may modify ischaemic cell changes by modulating somatostatin, a CNS neuropeptide that has been implicated in learning and memory [59]. The anti-oxidant effects of Salvia miltiorrhiza root have been

studied and several compounds have been identified with significant antioxidant activity. Such antioxidant compounds may be useful in AD therapy. Salvia leriifolia Benth (Lamiaceae) extract demonstrates antioxidant properties and cholinesterase inhibitory activity [60]. Cryptotanshinone, a compound from Salvia miltiorrhiza, modulates amyloid precursor protein metabolism and attenuates Abeta deposition through upregulating alpha-secretase in vivo and in vitro [61]. Tanshinones isolated from Salvia miltiorrhiza root have demonstrated antiinflammatory activity in mice and were active against 5-LOX in porcine leukocytes, but were not as active as the crude extracts. These activities need to be further investigated for confirmation, but could be relevant in AD therapy.

Withania somnifera (L.) Dun

Withania somnifera (Solanaceae) root (ashwagandha) is one of the most highly regarded herbs in Ayurvedic medicine and its use dates back almost 4000 years. It is classed among the rejuvenative tonics ('Rasayanas'). The herb is also traditionally used to treat inflammatory conditions, such as arthritis. Nicotine is reported to be present in Withania somnifera root. The presence of nicotine may explain the reputed activity of Withania somnifera in Ayurvedic medicine, considering that nicotine has been associated with cognitive enhancement and protection against AD development [62,63].There have been numerous studies regarding the cognitive enhancing activities of Withania somnifera. For example some steroidal derivatives that have been isolated from Withania somnifera root are the sitoindosides IX and X, which augmented learning acquisition and memory in both young and old rats. The extract containing the sitoindosides VII–X and withaferin A also reversed the ibotenic acid-induced cognitive deficit and reversed the reduction in cholinergic markers (e.g. ACh, ChAT) in rats [64]. These observations indicate that the sitoindosides VII–X and withaferin A could have potential in AD therapy. A root preparation of Withania somnifera has also been shown to significantly reduce the number of degenerating cells in the hippocampal region of stressed rats, which indicates the root extract may have potential neuroprotective effects in neurodegenerative disorders. Withania somnifera root, leaves and some constituents are also reported to have antioxidant and anti-inflammatory activities, inhibition of human acetyl cholinesterase [65] and protect the PC-12 cells from Abeta induced cell damage [66,67], which may also be relevant in AD therapy [68].

Conclusions

The treatment of AD remains a challenge in the modern medicine because of the pathogenesis of AD is a complex process involving both genetic and environmental factors; therefore development of effective disease-modifying drugs is proving to be a difficult task. These traditional Chinese medicines are regarded as new and promising sources of potential anti-AD drugs. These encouraging preclinical and clinical trials suggest that TCM is a promising candidate for the treatment of AD.

Abbreviations

AD: Alzheimer's disease; TCM: Traditional Chinese medicine; Abeta: Beta amyloid; APP: Amyloid precursor; HupA: Huperzine A; 3xTg-AD: Triple transgenic mice; MMSE: Mini-mental state examination; ADL: Activities of daily living scale; VaD: Vascular dementia; GEM: Ginkgo evaluation of memory; 5-HT: 5-Hydroxytryptamine; ChAT: Choline acetyltransferase; NGF: Nerve growth factor; NO: Nitric oxide.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Z-KS and H-QY made equal contributions to conception and design, acquisition of data, and in drafting the manuscript. S-DC was the general supervision of the research group, acquisition of funding, and involved in revising it critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

This study was supported by grants from the State Key Basic Research Program (No.2010CB945200), National "Twelfth Five-Year" Plan for Science & Technology Support (2012BAI10B03), Program for Outstanding Medical Academic Leader (No. LJ 06003), and Henan Key Science and Technology Project (No. 112102310684).

Author details

[1]Department of Neurology, Henan Provincial People's Hospital, Zhengzhou 450003Henan Province, People's Republic of China. [2]Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200025, People's Republic of China.

Received: 11 November 2012 Accepted: 15 February 2013
Published: 28 February 2013

References

1. Ved HS, Koenig ML, Dave JR, Doctor BP: **Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate.** *Neuroreport* 1997, **8**(4):963–968.
2. Wang R, Tang XC: **Neuroprotective effects of huperzine A: a natural cholinesterase inhibitor for the treatment of Alzheimer's disease.** *Neurosignals* 2005, **14**(1–2):71–82.
3. Yang L, Ye CY, Huang XT, Tang XC, Zhang HY: **Decreased accumulation of subcellular amyloid-beta with improved mitochondrial function mediates the neuroprotective effect of huperzine A.** *J Alzheimers Dis* 2012, **31**(1):131–142.
4. Wang Y, Tang XC, Zhang HY: **Huperzine A alleviates synaptic deficits and modulates amyloidogenic and nonamyloidogenic pathways in APPswe/PS1dE9 transgenic mice.** *J Neurosci Res* 2012, **90**(2):508–517.
5. Ratia M, Gimenez-Llort L, Camps P, Munoz-Torrero D, Perez B, Clos MV, Badia A: **Huprine X and huperzine a improve cognition and regulate some neurochemical processes related with Alzheimer's disease in triple transgenic mice(3xTg-AD).** *Neurodegener Dis* 2012, Epub ahead of print.
6. Wang CY, Zheng W, Wang T, Xie JW, Wang SL, Zhao BL, Teng WP, Wang ZY: **Huperzine a activates Wnt/beta-catenin signaling and enhances the nonamyloidogenic pathway in an alzheimer transgenic mouse model.** *Neuropsychopharmacology* 2011, **36**(5):1073–1089.
7. Wang BS, Wang H, Wei ZH, Song YY, Zhang L, Chen HZ: **Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis.** *J Neural Transm* 2009, **116**(4):457–465.
8. Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C, Jin S, Thomas R, Aisen PS: **A phase II trial of huperzine A in mild to moderate alzheimer disease.** *Neurology* 2011, **76**(16):1389–1394.

9. Zhang Z, Wang X, Chen Q, Shu L, Wang J, Shan G: **Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease, a placebo-controlled, double-blind, randomized trial.** *Zhonghua Yi Xue Za Zhi* 2002, **82**(14):941–944.
10. Topic B, Tani E, Tsiakitzis K, Kourounakis PN, Dere E, Hasenohrl RU, Hacker R, Mattern CM, Huston JP: **Enhanced maze performance and reduced oxidative stress by combined extracts of zingiber officinale and ginkgo biloba in the aged rat.** *Neurobiol Aging* 2002, **23**(1):135–143.
11. Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R: **The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid.** *Eur J Neurosci* 2000, **12**(6):1882–1890.
12. Yao Z, Drieu K, Papadopoulos V: **The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands.** *Brain Res* 2001, **889**(1–2):181–190.
13. Shi C, Wu F, Xu J: **H2O2 and PAF mediate Abeta1-42-induced Ca2+ dyshomeostasis that is blocked by EGb761.** *Neurochem Int* 2010, **56**(18): 893–905.
14. Stoll S, Scheuer K, Pohl O, Muller WE: **Ginkgo biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse.** *Pharmacopsychiatry* 1996, **29**(4):144–149.
15. Oken BS, Storzbach DM, Kaye JA: **The efficacy of ginkgo biloba on cognitive function in alzheimer disease.** *Arch Neurol* 1998, **55**(11):1409–1415.
16. Rigney U, Kimber S, Hindmarch I: **The effects of acute doses of standardized ginkgo biloba extract on memory and psychomotor performance in volunteers.** *Phytother Res* 1999, **13**(5):408–415.
17. Ihl R, Tribanek M, Bachinskaya N: **Efficacy and tolerability of a once daily formulation of ginkgo biloba extract EGb 761(R) in Alzheimer's disease and vascular dementia: results from a randomised controlled trial.** *Pharmacopsychiatry* 2012, **45**(2):41–46.
18. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM, DeKosky ST: **Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial.** *JAMA* 2009, **302**(24): 2663–2670.
19. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM: **Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo.** *J Biol Chem* 2005, **280**(7):5892–5901.
20. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL: **A potential role of the curry spice curcumin in alzheimer's disease.** *Curr Alzheimer Res* 2005, **2**(2):131–136.
21. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, Zaghi J, Badmaev V, Graves MC, Bernard G, Rosenthal M: **Curcuminoids enhance amyloid-beta uptake by macrophages of alzheimer's disease patients.** *J Alzheimers Dis* 2006, **10**(1):1–7.
22. Ishrat T, Hoda MN, Khan MB, Yousuf S, Ahmad M, Khan MM, Ahmad A, Islam F: **Amelioration of cognitive deficits and neurodegeneration by curcumin in rat model of sporadic dementia of Alzheimer's type (SDAT).** *Eur Neuropsychopharmacol* 2009, **19**(9):636–647.
23. Sun XK, Zhao YX, Ding JQ, Yang HQ, Qian K, Pan J, Lu GQ: **Inhibitory effect of Curcumin on apoptosis of PCI2 cells induced by amyloid 25–35.** *ShangHai Med J* 2007, **30**(11):843–846.
24. Wang HM, Zhao YX, Zhang S, Liu GD, Kang WY, Tang HD, Ding JQ, Chen SD: **PPARgamma agonist curcumin reduces the amyloid-beta-stimulated inflammatory responses in primary astrocytes.** *J Alzheimers Dis* 2010, **20**(4): 1189–1199.
25. Qin XY, Cheng Y, Yu LC: **Potential protection of curcumin against intracellular amyloid beta-induced toxicity in cultured rat prefrontal cortical neurons.** *Neurosci Lett* 2010, **480**(1):21–24.
26. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, Gylys K, Badmaev V, Heath D, Apostolova LG, Porter V, Vanek Z, Marshall GA, Hellemann G, Sugar C, Masterman D, Montine TJ, Cummings JL, Cole GM: **Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study.** *Alzheimers Res Ther* 2012, **4**(5):43. Epub ahead of print.
27. Zhang L, Yu H, Zhao X, Lin X, Tan C, Cao G, Wang Z: **Neuroprotective effects of salidroside against beta-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells.** *Neurochem Int* 2010, **57**(5):547–555.
28. Qu ZQ, Zhou Y, Zeng YS, Lin YK, Li Y, Zhong ZQ, Chan WY: **Protective effects of a rhodiola crenulata extract and salidroside on hippocampal neurogenesis against streptozotocin-induced neural injury in the rat.** *PLoS One* 2012, **7**(1):e29641.
29. Li QY, Wang HM, Wang ZQ, Ma JF, Ding JQ, Chen SD: **Salidroside attenuates hypoxia-induced abnormal processing of amyloid precursor protein by decreasing BACE1 expression in SH-SY5Y cells.** *Neurosci Lett* 2010, **481**(3):154–158.
30. Hoi CP, Ho YP, Baum L, Chow AH: **Neuroprotective effect of honokiol and magnolol, compounds from magnolia officinalis, on beta-amyloid -induced toxicity in PC12 cells.** *Phytother Res* 2010, **24**(10):1538–1542.
31. Erdo SL, Cai NS, Wolff JR, Kiss B: **Vinpocetin protects against excitotoxic cell death in primary cultures of rat cerebral cortex.** *Eur J Pharmacol* 1990, **187**(3):551–553.
32. Bonoczk P, Gulyas B, Adam-Vizi V, Nemes A, Karpati E, Kiss B, Kapas M, Szantay C, Koncz I, Zelles T, Vas A: **Role of sodium channel inhibition in neuroprotection: effect of vinpocetine.** *Brain Res Bull* 2000, **53**(3):245–254.
33. Deshmukh R, Sharma V, Mehan S, Sharma N, Bedi KL: **Amelioration of intracerebroventricular streptozotocin induced cognitive dysfunction and oxidative stress by vinpocetine–a PDE1 inhibitor.** *Eur J Pharmacol* 2009, **620**(1–3):49–56.
34. Szatmari SZ, Whitehouse PJ: **Vinpocetine for cognitive impairment and dementia.** *Cochrane Database Syst Rev* 2003, **1**:CD003119.
35. Akhondzadeh S, Abbasi SH: **Herbal medicine in the treatment of Alzheimer's disease.** *Am J Alzheimers Dis Other Demen* 2006, **21**(2):113–118.
36. Manyam BV: **Dementia in ayurveda.** *J Altern Complement Med* 1999, **5**(1):81–88.
37. Brinkhaus B, Lindner M, Schuppan D, Hahn EG: **Chemical, pharmacological and clinical profile of the East Asian medical plant centella asiatica.** *Phytomedicine* 2000, **7**(5):427–448.
38. Nalini K, Karanth KS, Rao A, Aroor AR: **Effects of piracetam on retention and biogenic amine turnover in albino rats.** *Pharmacol Biochem Behav* 1992, **42**(4):859–864.
39. Lee MK, Kim SR, Sung SH, Lim D, Kim H, Choi H, Park HK, Je S, Ki YC: **Asiatic acid derivatives protect cultured cortical neurons from glutamate-induced excitotoxicity.** *Res Commun Mol Pathol Pharmacol* 2000, **108**(1–2):75–86.
40. Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV: **Centella asiatica extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model.** *Phytother Res* 2009, **23**(1):14–19.
41. Veerendra Kumar MH, Gupta YK: **Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats.** *Clin Exp Pharmacol Physiol* 2003, **30**(5–6):336–342.
42. Tildesley NT, Kennedy DO, Perry EK, Ballard CG, Savelev S, Wesnes KA, Scholey AB: **Salvia lavandulaefolia (Spanish sage) enhances memory in healthy young volunteers.** *Pharmacol Biochem Behav* 2003, **75**(3):669–674.
43. Sadraei H, Ghannadi A, Malekshahi K: **Relaxant effect of essential oil of melissa officinalis and citral on rat ileum contractions.** *Fitoterapia* 2003, **74**(5):445–452.
44. Howes MJ, Perry NS, Houghton PJ: **Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders.** *Phytother Res* 2003, **17**(1):1–18.
45. Marongiu B, Porcedda S, Piras A, Rosa A, Deiana M, Dessi MA: **Antioxidant activity of supercritical extract of melissa officinalis subsp officinalis and melissa officinalis subsp inodora.** *Phytother Res* 2004, **18**(10):789–792.
46. Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E: **CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory.** *J Ethnopharmacol* 2000, **69**(2):105–114.
47. Iwasaki K, Satoh-Nakagawa T, Maruyama M, Monma Y, Nemoto M, Tomita N, Tanji H, Fujiwara H, Seki T, Fujii M, Arai H, Sasaki H: **A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients.** *J Clin Psychiatry* 2005, **66**(2):248–252.
48. Kennedy DO, Little W, Scholey AB: **Attenuation of laboratory-induced stress in humans after acute administration of melissa officinalis (lemon balm).** *Psychosom Med* 2004, **66**(4):607–613.
49. Kennedy DO, Wake G, Savelev S, Tildesley NT, Perry EK, Wesnes KA, Scholey AB: **Modulation of mood and cognitive performance following acute administration of single doses of melissa officinalis (lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties.** *Neuropsychopharmacology* 2003, **28**(10):1871–1881.
50. Cheng MC, Li CY, Ko HC, Ko FN, Lin YL, Wu TS: **Antidepressant principles of the roots of polygala tenuifolia.** *J Nat Prod* 2006, **69**(9):1305–1309.

51. Lv J, Jia H, Jiang Y, Ruan Y, Liu Z, Yue W, Beyreuther K, Tu P, Zhang D: **Tenuifolin, an extract derive d from tenuigenin, inhibits amyloid-beta secretion in vitro.** *Acta Physiol (Oxf)* 2009, **196**(4):419–425.
52. Nishiyama N, Zhou Y, Saito H: **Beneficial effects of DX-9386, a traditional Chinese prescription, on memory disorder produced by lesioning the amygdala in mice.** *Biol Pharm Bull* 1994, **17**(12):1679–1681.
53. Nishiyama N, Zhou Y, Saito H: **Ameliorative effects of chronic treatment using DX-9386, a traditional Chinese prescription, on learning performance and lipid peroxide content in senescence accelerated mouse.** *Biol Pharm Bull* 1994, **17**(11):1481–1484.
54. Tian J, Shi J, Zhang XK, Wang YY: **Herbal therapy: a new pathway of the treatment for Alzheimer's disease.** *Alzheimer's Res Ther* 2010, **2**(5):30–33.
55. Tian J, Shi J, Zhang L, Yin J, Hu Q, Xu Y, Sheng S, Wang P, Ren Y, Wang R, Wang Y: **GEPT extract reduces Abeta deposition by regulating the balance between production and degradation of Abeta in APPV717I transgenic mice.** *Curr Alzheimer Res* 2009, **6**(2):118–131.
56. Shi J, Tian J, Zhang X, Wei M, Yin L, Wang P, Wang Y: **A combination extract of ginseng, epimedium, polygala, and tuber curcumae increases synaptophysin expression in APPV717I transgenic mice.** *Chin Med* 2012, **7**(1):13.
57. Yabe T, Tuchida H, Kiyohara H, Takeda T, Yamada H: **Induction of NGF synthesis in astrocytes by onjisaponins of Polygala tenuifolia, constituents of kampo (Japanese herbal) medicine, Ninjin-yoei-to.** *Phytomedicine* 2003, **10**(2–3):106–114.
58. Kim JS, Narula AS, Jobin C: **Salvia miltiorrhiza water-soluble extract, but not its constituent salvianolic acid B, abrogates LPS-induced NF-kappaB signalling in intestinal epithelial cells.** *Clin Exp Immunol* 2005, **141**(2):288–297.
59. Kuang P, Wu W, Zhu K: **Evidence for amelioration of cellular damage in ischemic rat brain by radix salviae miltiorrhizae treatment–immunocytochemistry and histopathology studies.** *J Tradit Chin Med* 1993, **13**(1):38–41.
60. Loizzo MR, Tundis R, Conforti F, Menichini F, Bonesi M, Nadjafi F, Frega NG: **Salvia leriifolia Benth (Lamiaceae) extract demonstrates in vitro antioxidant properties and cholinesterase inhibitory activity.** *Nutr Res* 2010, **30**(12):823–830.
61. Mei Z, Zhang F, Tao L, Zheng W, Cao Y, Wang Z, Tang S, Le K, Chen S, Pi R, Liu P: **Cryptotanshinone, a compound from Salvia miltiorrhiza modulates amyloid precursor protein metabolism and attenuates beta-amyloid deposition through upregulating alpha-secretase in vivo and in vitro.** *Neurosci Lett* 2009, **452**(2):90–95.
62. Newhouse PA, Kelton M: **Nicotinic systems in central nervous systems disease: degenerative disorders and beyond.** *Pharm Acta Helv* 2000, **74**(2–3):91–101.
63. van Duijn CM, Hofman A: **Relation between nicotine intake and Alzheimer's disease.** *BMJ* 1991, **302**(6791):1491–1494.
64. Matsuda H, Murakami T, Kishi A, Yoshikawa M: **Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of Indian Withania somnifera DUNAL and inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum.** *Bioorg Med Chem* 2001, **9**(6):1499–1507.
65. Grover A, Shandilya A, Agrawal V, Bisaria VS, Sundar D: **Computational evidence to inhibition of human acetyl cholinesterase by withanolide a for alzheimer treatment.** *J Biomol Struct Dyn* 2012, **29**(4):651–662.
66. Jayaprakasam B, Padmanabhan K, Nair MG: **Withanamides in Withania somnifera fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease.** *Phytother Res* 2010, **24**(6):859–863.
67. Kumar S, Seal CJ, Howes MJ, Kite GC, Okello EJ: **In vitro protective effects of Withania somnifera (L) dunal root extract against hydrogen peroxide and beta-amyloid(1–42)-induced cytotoxicity in differentiated PC12 cells.** *Phytother Res* 2010, **24**(10):1567–1574.
68. Rasool M, Varalakshmi P: **Protective effect of Withania somnifera root powder in relation to lipid peroxidation, antioxidant status, glycoproteins and bone collagen on adjuvant-induced arthritis in rats.** *Fundam Clin Pharmacol* 2007, **21**(2):157–164.

doi:10.1186/2047-9158-2-6
Cite this article as: Sun *et al.*: Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease. *Translational Neurodegeneration* 2013 **2**:6.